Her2/neu Protein Expression and Oncogene Amplification in Gastric Carcinoma in Egyptian patients

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by:

Ranya Abdel Rahman Ebrahim Al Ashiry

M. Sc of pathology, Faculty of Medicine, Cairo University

Under Supervision of:

Prof. Dr. Ali Ahmed El Hindawi

Professor of Pathology, Faculty of Medicine, Cairo University

Prof. Dr. Ahmed Mahmoud Abdel Hadi

Professor of Pathology, Theodor Bilharz Research Institute

Dr. Amal Ahmed Mohamed Hareedy

Lecturer of Pathology, Faculty of Medicine, Cairo University

Faculty of Medicine

Cairo University

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ABSTRACT

BACKGROUND

Gastric cancer (GC) is a major cause of cancer death worldwide, especially in the developing countries. In Egypt, GC is the 12th most common cancer in both sexes representing 1.6% of the total cancers. It is the 12th leading cause of cancer death representing 2.2% of the total cancer mortality. Amplification of the Her2/neu gene and overexpression of the Her2/neu protein in GC is a golden criterion for target therapy with trastuzumab (Herceptin).

MATERIAL AND METHODS

Eighty five formalin-fixed and paraffin-embedded tumor tissue samples from Egyptian gastric carcinoma patients were studied for Her2/neu with immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) methods. Thirty cases of non-malignant lesions (Gastritis, intestinal metaplasia, adenoma with low grade dysplasia, adenoma with high grade dysplasia) were studied with IHC. Associations between clinicopathological factors and Her2/neu positivity were done.

RESULTS

Twenty three cases (27%) were defined as positive for Her2/neu gene amplification and/or protein overexpression. The levels of Her2/neu positive (3+), Her2/neu equivocal (2+) and Her2/neu negative (1+/0) were measurable in 14.2%, 32.9% and 52.9% of the samples, respectively. FISH showed that Her2/neu gene was amplified in 22 cases,

10 Her2/neu positive (3+), 11 (39.3%) Her2/neu equivocal (2+) and 1 Her2/neu negative (1+) cases with IHC staining. There was a higher Her2/neu positivity (3+) in intestinal type and mixed carcinoma, and moderately differentiated tumors.

None of the gastritis, intestinal metaplasia or adenoma with low grade dysplasia cases showed positivity for Her2/neu (3+). The Her2/neu positivity (3+) was associated with both adenocarcinoma cases and high grade dysplasia ($P = 0.002$).

CONCLUSION:

Her2/neu expression in Egyptian patients was comparable to that in other populations; 27% of Egyptian patients with primary GC and GEJ adenocarcinoma were Her2/neu-positive on IHC and FISH. Her2/neu positivity (3+) was common in the mixed, intestinal type and moderately differentiated carcinoma. The results highlight the necessity of FISH test for further categorization when gastric cancer cases are equivocal (2+) by IHC to determine eligibility for the targeted therapy. Stepwise increase in the expression of Her2/neu was seen in low grade dysplasia, high grade dysplasia and carcinoma cases implying its role in cancer evolution.

Key words:
Egyptian; Gastric cancer; Gastroesophageal cancer; Her2/neu; Protein expression (IHC); Gene amplification (FISH).

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List of abbreviations

5-FU	5-fluorouracil drug
AJCC	American Joint Committee on Cancer
ASCO-CAP	The American Society of Clinical Oncology/College of American Pathologists.
ATP	Adenosine Triphosphate
Bax	BCL2-associated X protein
BC	Before Christ
Bcl-2	B-cell CLL/lymphoma 2
Bcl-6	B-cell CLL/lymphoma 6
BRCA1/2	Breast cancer gene
CA IX	Carbonic anhydrase IX
CagA	Cytotoxin-associated gene A
CEA	Carcinoembryonic antigen
CISH	Chromogenicin situ hybridization
c-myc2	Cellular myelocytomatosis 2
COX-2	Cytochrome Oxidase Subunit 2
CT	Computed tomography
D-GC	Diffuse type gastric cancer
DISH	Dual-color in situhybridization
EEA-EFTA	The European Economic Area / European Free Trade Association
EGFR	Human epidermal growth factor receptor
EMR	Endoscopic mucosal resection
ERK	Extracellular signal-regulated kinase
EUS	Endoscopic ultrasound
FAP	Familial adenomatous polyposis
FDA/CAP	Food & Drug Administration/College of American Pathologists
FDG	F-Fluorodeoxyglucose
FDG-PET	F-Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET)
FISH	Fluorescence in situ hybridization
GC	Gastric cancer
GEJ /EGJ	Gastro-esophageal junction
GERD	Gastroesophageal reflux disease
H & E	Hematoxylin and eosin stain
H. pylori	Helicobacter pylori microorganism
HDGC	Hereditary diffuse gastric cancer
Her2/neu	Human epidermal growth factor receptor 2
HNPCC	Hereditary nonpolyposis colon cancer syndrome

ICD-O	The International Classification of Diseases for Oncology
I-GC	Intestinal type gastric cancer
IHC	Immunohistochemistry
KLF5	Kruppel Like Factor 5
MAPK	Mitogen-activated protein kinase
MMP-2	MMP2 matrix metallopeptidase 2
Mortality ASR	Mortality Age-Standardized Rate (oncology)
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NBI	Magnifying endoscopy with narrow-band imaging
OS	Overall survival
PET	Positron Emission Tomography
PI3K	Phosphoinositide 3-Kinase
PKP3	Plakophilin-3
ROS	Reactive oxygen species
RT	Radiation therapy
RTKs	Receptor tyrosin-kinases
SATB1	SATB homeobox 1
SISH	Silver in situ hybridization
TGF β	Transforming Growth Factor beta
TNM	The tumor-node-metastasis system
ToGA trail	Trastuzumab for GAstric cancer trial
TOP2A	Topoisomerase II alpha
VEGF	Vascular Endothelial Growth Factor
WHO/IARC	World Health Organization International Agency for Research on Cancer

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